

Spectral analysis of wakefulness and REM sleep EEG in patients with sleep apnoea syndrome

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Spectral analysis of wakefulness and REM sleep EEG in patients with sleep apnoea syndrome. F. Morisson, G. Lavigne, D. Petit, T. Nielsen, J. Malo, J. Montplaisir. ©ERS Journals Ltd 1998.

ABSTRACT: Neuropsychological investigations of patients with obstructive sleep apnoea syndrome (OSAS) have shown impairments in such basic functions as memory, attention and executive control. Since executive functions are known to be dependent on the integrity of the frontal lobe, it was hypothesized that OSAS may be associated with hypoxaemic frontal lobe dysfunction.

To test this hypothesis, 21 apnoeic patients and 10 normal controls were studied with quantitative electroencephalographic (EEG) methods during rapid eye movement (REM) sleep, when most apnoeic events occur and during wakefulness.

In apnoeic patients, EEG slowing in REM sleep was observed over frontal, central and parietal regions, while EEG slowing during wakefulness was observed over all cortical regions examined. A positive correlation was found between EEG slowing during wakefulness and oxygen desaturation during the night.

Contrary to the hypothesis, these electroencephalographic changes were not localized only to the frontal region. This result may explain the wide range of neuropsychological deficits noted in patients with obstructive sleep apnoea syndrome, in addition to their poor performance in tasks of executive functioning.

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Obstructive sleep apnoea syndrome (OSAS) is a condition characterized by repetitive cessation of breathing during sleep due to obstruction of the upper airway. Nocturnal manifestations of OSAS include periodic snoring, sleep fragmentation, nocturnal hypoxaemia and cardiac arrhythmia, which may lead to sudden death during sleep [1]. During the day, OSAS patients complain of excessive daytime sleepiness (EDS) and decreased cognitive performance [1–8].

There are disagreements in the literature concerning the factors responsible for cognitive deficits observed in OSAS. Both daytime sleepiness and nocturnal hypoxaemia have been found to contribute to these deficits. Decreased cognitive performance was first attributed to daytime somnolence resulting from disrupted nocturnal sleep [9, 10], although several studies have since shown that nocturnal hypoxaemia is also an important contributing factor [3, 11–14]. Studies of patients with various degrees of EDS and hypoxaemia suggest that deficits in executive and psychomotor tests are more closely associated with the severity of hypoxaemia, while attention and memory deficits are more strongly related to vigilance impairment [8, 14].

"Executive" functions, including planning, programming, regulation and verification of goal-directed behaviour, are known to be dependent on the integrity of the frontal lobe [15]. Thus, it was hypothesized that OSAS may be associated with hypoxaemic frontal lobe dysfunction [8]. Quantitative electroencephalographic analysis (qEEG) was used to assess potential frontal lobe dysfunction in OSAS patients. The qEEG has been found to be useful in the classification of vascular and degenerative dementia [16–20].

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The first hypothesis of the present study was that OSAS patients would show EEG slowing preferentially in the frontal regions, not only during rapid eye movement (REM) sleep, when most apnoeic events occur, but also during wakefulness when cognitive impairments are seen. The second hypothesis was that EEG slowing in the frontal region would be correlated with nocturnal hypoxaemia (time in minutes spent with the arterial oxygen saturation (S_{a,O_2}) <90%).

Methods

Subjects

The study included 21 patients with OSAS, 19 males and two females, aged 34–57 yrs (mean±SD 44±7 yrs). None of the patients had ever been treated with nasal continuous positive airway pressure (CPAP). Inclusion criteria for this group were an apnoea-hypopnoea index (AHI) >10 events·h⁻¹ of sleep and a minimum oxygen saturation <80%. Ten normal subjects, nine males and one female, aged 36–55 yrs (mean±SD 44±6 yrs) served as a control group. They had no clinical evidence of snoring or sleep apnoea and no complaint of EDS. They all had an AHI <5 events·h⁻¹ of sleep, a microarousal index <10 events·h⁻¹ of sleep and a mean sleep latency on the multiple sleep latency test (MSLT) >10 min. Normal subjects were recruited by advertising in local newspapers and they were paid for their participation. Normal subjects were matched for age

and education but not for body mass index, since it was virtually impossible to find obese normal controls who did not snore or have sleep apnoeas.

Exclusion criteria for both groups were a history of cerebral insult of any aetiology, a history of other sleep disorders or pulmonary diseases, the presence of a neurological or psychiatric condition, a history of excessive alcohol consumption or drug misuse, and the use of any medication known to influence sleep, EEG or respiratory function in the month prior to entering the study. Informed consent was obtained from every subject who participated.

Experimental procedures

Polygraphic recordings. All subjects were monitored for 36 h in the sleep laboratory, including two consecutive nights with the MSLT performed during the intervening day. The first night was for adaptation to the sleep laboratory conditions and only data obtained during the second night were analysed. A thoracoabdominal plethysmograph and oral and nasal thermistors were used to monitor respiration. S_{a,O_2} during sleep was measured continuously at 2 s intervals by a transcutaneous finger pulse oximeter. Sleep was recorded and scored according to the method of RECHSCHMANN and KAIS [21]. Sleep latency was defined as the time from lights out to the occurrence of one consecutive minute of stage 1 sleep or one epoch of any other sleep stage. REM efficiency represents the percentage of time spent in REM sleep over the total duration of the REM sleep period, defined as all REM sleep epochs separated by intervals <15 min. Microarousals were also scored; they were defined as abrupt shifts in EEG frequency which may include θ , α and/or frequencies >16 Hz, but not spindles [22]. Electromyography from right and left anterior tibialis muscles was recorded to score periodic leg movements during sleep (PLMS). Movements of 0.5–5 s in duration, separated by intervals of 4–90 s and occurring in series of four consecutive movements, were scored as PLMS [23].

Several respiratory parameters were measured. An apnoea was defined as total cessation of airflow lasting for at least 10 s [24]. An hypopnoea was defined as a reduction in airflow of at least 50% from baseline, lasting at least 10 s, measured by thermistors at the nose and mouth [25]. The AHI was defined as the number of apnoeas and hypopnoeas per hour of sleep. Hypoxaemia severity was estimated by the mean duration of respiratory events (apnoeas and hypopnoeas), the minimal S_{a,O_2} value recorded during sleep, and the sleep time spent in minutes with S_{a,O_2} <80% and <90%.

Daytime sleepiness was assessed by the MSLT [26]. The mean sleep latency for five naps scheduled at 2 h intervals starting at 10:00 h was calculated and used as an index of sleepiness. Each nap was terminated at sleep onset or after 20 min if the subject did not fall asleep.

EEG recordings and analyses. EEG electrodes were positioned according to the International 10–20 System [27]. Recordings were obtained from the following leads: Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T3, T4, T5 and T6, in reference to linked ears. EEG signals were recorded on a 24-channel Grass Model 12–32 polygraph (bandpass, 0.3–100 Hz) (Grass Instruments, Quincy, MA, USA). EEG signals were digitized at a rate of 256 Hz and

filtered with a digital filter (cut-off frequency 64 Hz). Every second data point was saved on disk (128 Hz).

For approximately 10 min starting at 07:00 h on the second morning, samples of the awake EEG were recorded while subjects were lying in bed with their eyes closed. To prevent drowsiness, they were asked to open their eyes every minute or when a signal of sleepiness appeared on the tracing (*e.g.* slow rolling eye movements). For each subject, 24 mini-epochs of artefact-free 4 s sections were selected for a total sample size of 96 s. REM sleep EEG samples were selected from artefact-free EEG sections positioned between two bursts of REM. These samples were all selected during apnoeic pauses since in most OSAS patients it was virtually impossible to sample REM sleep EEG without apnoeic events. The EEG was sampled in the middle of the apnoeas and special care was taken to avoid EEG changes associated with arousals that occurred towards the end of the apnoeic episodes. As for wakefulness, the total sample size of REM sleep EEG was 96 s. Amplitude spectral analyses were performed using a commercial software package [28] which calculates the fast Fourier transform on 4 s mini-epochs with a resolution of 0.25 Hz and a cosine window smoothing. Four frequency bands were defined as δ (0.75–3.75 Hz), θ (4.00–7.75 Hz), α (8.00–12.75 Hz) and β (13.00–20.25 Hz). The ratio of slow frequencies ($\delta+\theta$: $\delta\theta$) to fast frequencies ($\alpha+\beta$: $\alpha\beta$) was selected as a global index of EEG slowing (*i.e.* $\delta\theta/\alpha\beta$) during both states [16]. Changes in the $\delta\theta/\alpha\beta$ ratio could reflect EEG slowing due to an increase in slow frequencies, a decrease in fast frequencies, or both. The absolute power in each frequency band was also calculated. As non-REM sleep is a very heterogeneous state, samples of non-REM EEG were not studied. Not only are there several non-REM stages (stages 1, 2, 3 and 4) but each of these shows important variability. For example, some sections of stage 2 sleep are characterized by θ activity, k-complex and sleep spindles, while others are also characterized by a considerable amount of δ activity (between 0–20%). Therefore, EEG spectral analysis will give different results depending on the stage sampled. This is particularly important in sleep apnoea patients, whose sleep structure is dramatically different from normal subjects.

Statistical analyses

Tests of normality were performed on EEG indices. Student's t-tests were used for between-group comparisons of variables with normal distributions (with pooled variance or separate variance estimates depending on the results of homogeneity tests), otherwise the nonparametric equivalent, the Mann-Whitney U-test, was used. Relationships between respiratory (time with S_{a,O_2} <90%), polygraphic (mean sleep latency on the MSLT and qEEG ($\delta\theta/\alpha\beta$ ratio for all regions pooled and for the frontal region only) variables were measured with Pearson product-moment correlations for apnoeic patients only (n=21).

Results

Demographic, respiratory and polysomnographic variables

There was no age difference between groups. However, they clearly differed in body mass index and all

sleep-state respiratory variables (table 1). As shown in table 2, apnoeic patients had lower percentages of slow-wave and REM sleep, a lower REM sleep efficiency, a higher percentage of stage 1 sleep, and higher micro-arousal and PLMS indices than did control subjects. Apnoeic patients were also sleepier than normal controls during the daytime, as measured by the MSLT. Total sleep time, percentage of stage 2 sleep and sleep efficiency were comparable in both groups.

Spectral analyses

Compared to normal controls, apnoeic patients showed EEG slowing (*i.e.* a higher ($\delta\theta/\alpha\beta$) ratio) during REM sleep and during wakefulness for all regions pooled ($p < 0.05$ for REM sleep and $p < 0.01$ for wakefulness; table 3). Figure 1 shows between-group comparisons for each of the five regions studied during REM sleep (fig. 1a) and during wakefulness (fig. 1b). The $\delta\theta/\alpha\beta$ ratio for each of the five regions represents the mean of several EEG leads: Fp1, Fp2, F3, F4, F7 and F8 for the frontal region, C3 and C4 for the central region, P3 and P4 for the parietal region, O1 and O2 for the occipital region and T3, T4, T5 and T6 for the temporal region.

Table 1. – Sociodemographic and respiratory variables for apnoeic patients and controls

	Controls mean (SD)	Apnoeics mean (SD)	p-value
Sociodemographic features			
Sex F/M	1/9	2/19	
Age yrs	44 (6)	44 (7)	NS
Body mass index	26.1 (3.8)	40.7 (6.0)	<0.001*
Respiratory variables			
Minimal Sa _a O ₂ value %	87.7 (4.6)	61.4 (12.9)	<0.001+
Time with Sa _a O ₂ <80% min	0	52.2 (76.4)	<0.001#
Time with Sa _a O ₂ <90% min	0.7 (1.5)	216.9 (181.6)	<0.001#
Sleep apnoea-hypopnoea index events·h ⁻¹	0.6 (0.6)	62.9 (26.1)	<0.001+
Mean duration of apnoea s	0	22.9 (4.7)	<0.001+

F: female; M: male; Sa_aO₂: arterial oxygen saturation. *: t-test for pooled variances; +: t-test for separate variances; #: Mann-Whitney U-test. NS: nonsignificant.

Table 2. – Polysomnographic variables for apnoeic patients and controls

	Controls mean (SD)	Apnoeics mean (SD)	p-value
Polysomnographic variables			
Total sleep time min	419.9 (53.4)	416.7 (45.0)	NS
Stage 1 sleep %	11.0 (3.5)	19.7 (9.8)	0.007#
Stage 2 sleep %	60.2 (7.1)	63.8 (8.0)	NS
Slow-wave sleep %	7.5 (6.6)	2.7 (3.3)	0.04#
REM sleep %	21.2 (2.5)	14.2 (4.7)	<0.001#
Microarousal index events·h ⁻¹	6.7 (1.9)	37.2 (22.1)	<0.001#
PLMS index events·h ⁻¹	0.7 (0.3)	34.2 (30.0)	<0.001#
Sleep efficiency %	85.8 (6.4)	88.1 (6.3)	NS
REM efficiency %	84.6 (7.2)	59.5 (24.3)	<0.001#
MSLT: mean latency min	13.1 (2.5)	4.5 (2.3)	<0.001*

REM: rapid eye movement; PLMS: periodic leg movements during sleep; MSLT: multiple sleep latency test. *: t-test for pooled variance; #: Mann-Whitney U-test. NS: nonsignificant.

Table 3. – Between-group comparisons for electroencephalography (EEG) slowing ratio

qEEG	Controls mean (SD)	Apnoeics mean (SD)	p-value
Wakefulness $\delta\theta/\alpha\beta$ ratio	0.70 (0.12)	0.89 (0.27)	0.009*
REM sleep $\delta\theta/\alpha\beta$ ratio	1.40 (0.19)	1.59 (0.25)	0.05*

qEEG: quantitative EEG; REM: rapid eye movement. *: t-test for pooled variances.

The EEG slowing observed during REM sleep was significant for the frontal region (fig. 1a). During wakefulness, EEG activity in all five regions was significantly slower in the apnoeic group (fig. 1b).

Figure 2 shows the breakdown of the REM sleep EEG slowing ratio into individual frequency bands by region for the OSAS and control groups. Absolute δ activity was significantly greater in the frontal region for OSAS patients ($p=0.01$).

In wakefulness absolute δ activity was significantly greater in the frontal region only for OSAS patients ($p=0.02$), although absolute δ activity was nonsignificantly higher in all other regions (fig. 3). Absolute θ activity was greater in all regions but the difference was significant only for the frontal region ($p=0.03$).

Since there was no between-group difference in total EEG power (mean±SD=223±47.7 μV^2 versus 240±61.3 μV^2 for the controls and the apnoeic subjects, respectively, during wakefulness; 172±27.7 μV^2 versus 177±28.9

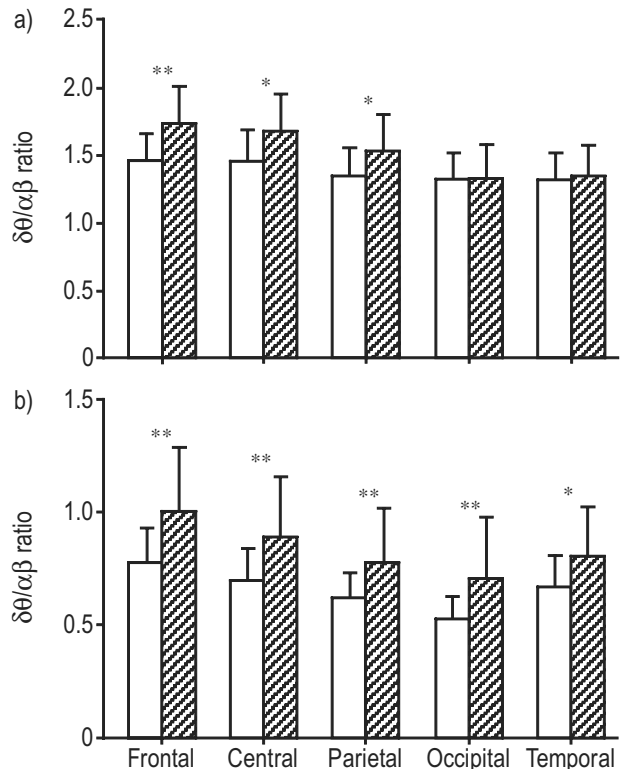


Fig. 1. – Ratio of slow ($\delta+\theta$: $\delta\theta$) to fast ($\alpha+\beta$: $\alpha\beta$) activity in the five cortical regions during: a) rapid eye movement sleep; and b) wakefulness for controls (□) and apnoeic patients (▨). Values are shown as mean±SD. *: $p < 0.05$; **: $p < 0.01$ by Student's t-test.

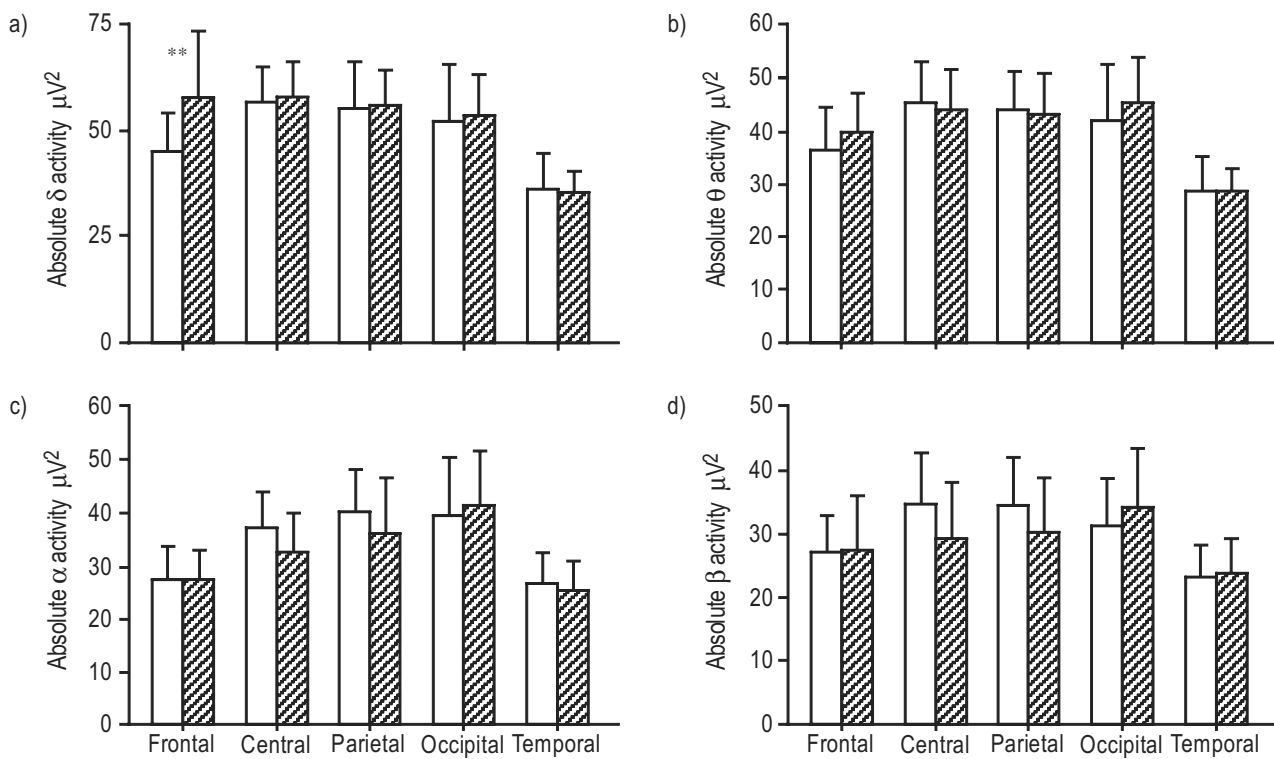


Fig. 2. - Rapid eye movement sleep absolute activity in the five cortical regions for: a) δ ; b) θ ; c) α ; and d) β for controls (▨) and apnoeic patients (□). Values are shown as mean \pm SD. **: $p \leq 0.01$ by Student's t-test.

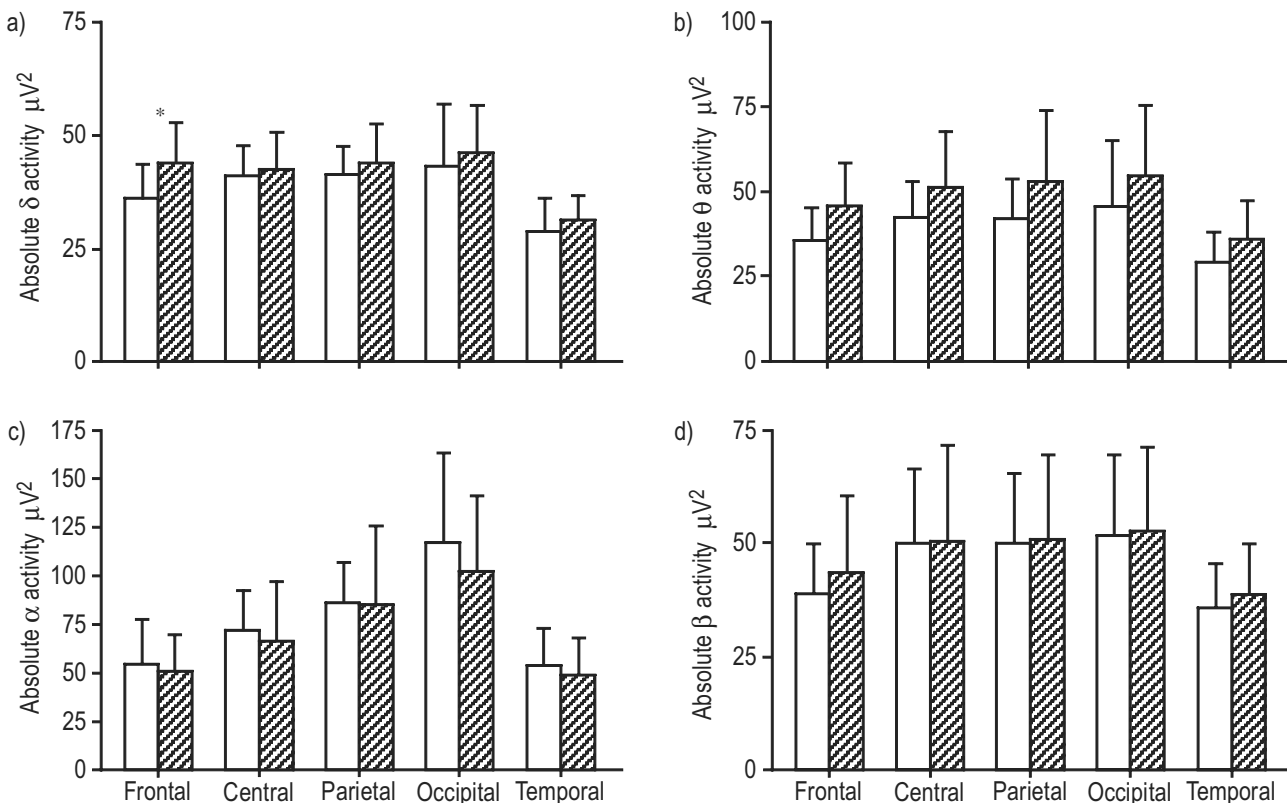


Fig. 3. - Wakefulness absolute activity in the five cortical regions for: a) δ ; b) θ ; c) α ; and d) β for controls (▨) and apnoeic patients (□). Values are shown as mean \pm SD. *: $p \leq 0.05$ by Student's t-test.

μV^2 for the controls and the apnoeic subjects, respectively, during REM sleep), the observed changes in absolute activity in the apnoeic group are not attributable to morphological differences such as bone density, bone thickness, head size or brain volume.

Correlation between qEEG, nocturnal hypoxaemia and daytime somnolence

A positive correlation was found between the $\delta\theta/\alpha\beta$ ratio (all regions) during wakefulness and nocturnal hypoxaemia, *i.e.* time with $S_{a,O_2} < 90\%$, ($r=0.45$; $p=0.043$). However, the correlation is no longer significant if the Bonferroni correction is applied to take into account the number of correlations made ($n=16$). This ratio did not correlate with mean sleep latency on the MSLT ($r=-0.21$; $p=0.35$).

For REM sleep, no correlation was found between the $\delta\theta/\alpha\beta$ ratio and the time spent with $S_{a,O_2} < 90\%$ ($r=0.02$, $p=0.92$) or between the ratio and mean sleep latency on the MSLT measured on the following day ($r=-0.21$, $p=0.36$).

Discussion

Nocturnal sleep disruption in OSAS

The results of the present study are in agreement with a large amount of literature showing nocturnal sleep disruption and EDS in OSAS patients. Patients in the present study were severely affected: they were characterized by a mean AHI of 62.9 and a mean time spent with nocturnal $S_{a,O_2} < 90\%$ of 217 min. Severity of OSAS should be evaluated carefully when comparing the results of neuropsychological or electrophysiological testing in apnoeic patients.

Slowing of the REM sleep EEG in patients with OSAS

In REM sleep, EEG slowing was found in the frontal region in patients with OSAS. To our knowledge, this is the first study comparing qEEG of OSAS patients and normal control subjects during REM sleep and during wakefulness. One study [29] of four apnoeic patients and three normal controls found a decrease in activity in the θ , α and β bands (the δ band is not mentioned) during stage 2 sleep with apnoeas relative to stage 2 sleep without apnoeas. However, no measurements were made in REM sleep or during wakefulness, only topographical brain maps were presented, exact absolute and relative power values were not reported and no statistical comparisons were provided.

The results suggest that the REM sleep EEG of apnoeics is characterized by an increased ratio of slow to fast activity, which is mostly due to an increase in δ activity in the frontal regions. Slow EEG activity has often been construed as a sign of arousal in the context of obstructive apnoea. Bursts of δ activity occurring at the end of the apnoeas or upon the resumption of breathing, especially during non-REM sleep, were noted in a previous study [30]. The finding of an increase in δ activity (during REM sleep) is probably not a manifestation of EEG arousal since the EEG was never sampled towards the end of

the apnoeic episode. Since the REM sleep EEG was analysed for apnoeic episodes in OSAS patients and for non-apnoeic episodes in normal controls, one may question whether movement artefacts may have contributed to the increase in slow frequencies noted in apnoeic patients. Indeed, respiratory efforts by apnoeic patients may have generated undetected body movements which, in turn, may have influenced EEG recordings. This possibility cannot be completely ruled out. However, REM sleep EEG was also sampled outside apnoea episodes in three patients and the results showed an increase in the $\delta\theta/\alpha\beta$ ratio (1.49 ± 0.19) similar to that seen in REM sleep EEG during apnoeas (1.59 ± 0.27). No correlation was found between REM sleep EEG slowing and degree of oxygen desaturation (time with $S_{a,O_2} < 90\%$). These results indicate that EEG slowing in REM sleep is not the direct consequence of a transient desaturation taking place during the apnoeic event itself. This is in agreement with the results of SVANBERG and GUILLEMNALT [31], who did not find a progressive increase in δ activity during the course of apnoeas occurring in REM sleep.

Further studies should verify whether the EEG slowing during REM sleep is alleviated by treatment of apnoeas with nasal continuous positive airway pressure.

EEG slowing during wakefulness

To our knowledge, the present study shows for the first time a slowing of the EEG during wakefulness in OSAS patients. These EEG changes were positively correlated with the degree of oxygen desaturation during the previous night.

Although EEG slowing during wakefulness may have resulted from increased sleepiness, several observations make this interpretation unlikely. Firstly, patients were carefully monitored and instructed to maintain a high level of vigilance during EEG collection in the waking state. Indeed, no polygraphic signs of sleepiness, such as slow rolling eye movements, were seen on the tracings. Secondly, no correlations were found between qEEG variables and mean sleep latency on the MSLT. Thirdly, distinct patterns of EEG slowing are found in normal drowsy subjects and in patients with OSAS. BRUCHON and HASNI [32] reported that in many subjects the first EEG sign of drowsiness was the presence of a slower α frequency in frontal and central areas, falling off in the parietal region and of low amplitude or absent altogether in the occipital region. They also noted increased θ activity, which was usually centrally distributed. In the present study, apnoeic patients did not show this drowsy EEG pattern: δ and θ activity was increased over the frontal region and α activity was not significantly decreased in the occipital region.

Other observations suggest that nocturnal hypoxaemia may play a role in slowing of the EEG during wakefulness. For example, waking EEG patterns of apnoeic patients have many similarities with EEG changes in normal subjects under hypobaric hypoxia [33], where increased slow activity and decreased α and β activities are observed. The significant correlation found in the present study between EEG changes during wakefulness and the degree of nocturnal oxygen desaturation further supports the hypothesis that nocturnal hypoxaemia rather than sleepiness is the primary factor involved in EEG slowing during wakefulness in OSAS. However, it should be noted that

the correlation between slowing of the EEG and oxygen desaturation was only weak ($r=0.45$, $p=0.043$). Considering the large number of correlations examined ($n=16$), we cannot exclude the possibility that this correlation has arisen by chance.

Contrary to our hypothesis, the electroencephalographic changes seen in the present study were not localized only to the frontal region. This result may help to explain the wide range of neuropsychological deficits noted in obstructive sleep apnoea syndrome patients, not only their poor performance on executive function tasks. Further studies should investigate correlations between quantitative electroencephalographic changes in various brain regions and specific neuropsychological deficits in obstructive sleep apnoea syndrome patients. Reassessment of patients after treatment with nasal continuous positive airway pressure would also help to determine whether electroencephalographic slowing is the consequence of anoxic brain dysfunction or a sign of possible irreversible brain damage.

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